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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,065	BRASCH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/16/2005* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20, 27, and 30-79* is/are pending in the application.

4a) Of the above claim(s) *40-43, 52-55, 60-68, and 71-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20, 27, 32--39, 44-51, 56-59, 69, and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2001* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of species (1) (claims 58, 59, 69, and 70) in the reply filed on December 16, 2005 is acknowledged. The traversal is on the ground(s) that "[I]n the Office Action at page 2, the Examiner states that the claims are directed to patentably distinct species. However, even where patentably distinct inventions appear in a single application, restriction remains improper unless the Examiner can show that the search and examination of the groups would entail a 'serious burden.' See MPEP § 803. In the present situation, the Examiner has failed to make such a showing".

The above arguments have been fully considered and have not been found persuasive toward the withdrawal of the restriction requirement nor persuasive toward the relaxation of same such that species (1) to (10) will be examined together. First, there is a search burden on the examiner to search all species because species (1) to (10) are directed to different mobile genetic elements. Second, applicant has no evidence to show that searching one species can find all 10 different species. Third, MPEP § 809.02(a) states: "[S]hould applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention". However, applicant does not submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. For example, applicant does not submit evidence to show that species

(1) is an obvious variant of species (2) to (10). Therefore, the requirement is still deemed proper and is therefore made FINAL. Claims 14-20, 27, 32-39, 44-51, 56-59, 69, and 70 will be examined.

Claim Objections

2. Claims 34, 35, and 47 are objected to because of the following informality: "an integrating virus" should be "a sequence from an integrating virus".

3. Claims 58 and 69 are objected to because of the following informality: "integrating viruses" should be "sequences from integrating viruses".

Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 14-20, 27, 32, 33, 44-46, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer (US Patent No. 5,605,793, published by February 25, 1997).

Stemmer teaches method for *in vitro* recombination which can be used in many different genes encoded proteins.

Regarding claim 14, according to the specification, integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein" is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches inserting one or more double-stranded oligonucleotides comprising one or more mutations into double-stranded random fragments, denaturing the resultant mixture of the double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which results in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide (see column 3, second paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in claim 14. Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer are inserted into one or more double-stranded random fragments in

the presence of a polymerase and form a mutagenized double-stranded polynucleotide, one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer contain one or more recombination sites as recited in claim 14. Therefore, Stemmer discloses inserting one or more integration sequences (ie., one or more double-stranded oligonucleotides comprising one or more mutations) comprising at least one recombination site into at least one nucleic acid molecule (ie., double-stranded random fragments) to produce one or more integration sequence-containing nucleic acid molecules as recited in claim 14. Since the mutagenized double-stranded polynucleotide taught by Stemmer is cloned into an appropriate vector (see column 8, lines 60 and 61) and it is known that a cloning process must used a ligase, according to the definition of "recombination protein" in the specification, a ligase is a recombination protein and Stemmer discloses transferring one or more integration sequence-containing nucleic acid molecules formed in the inserting step comprising at one recombination site into one or more vectors in the presence of one or more recombination proteins (ie., a ligase) as recited in claim 14.

Regarding claims 16 and 18, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches inserting one or more double-stranded oligonucleotides

comprising one or more mutations into double-stranded random fragments, denaturing the resultant mixture of the double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which result in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide (see column 3, second paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in claim 16. Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer are inserted into one or more double-stranded random fragments in the presence of a polymerase and form a mutagenized double-stranded polynucleotide, one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer contain one or more recombination sites as recited in claim 16. Therefore, Stemmer discloses inserting one or more integration sequences (ie., one or more double-stranded oligonucleotides comprising one or more mutations) comprising at least one recombination site into at least one nucleic acid molecule (ie., double-stranded random fragments) as recited in claim 16. Since, after restriction digestion, the digested mutagenized double-stranded polynucleotide taught by Stemmer is cloned into an appropriate vector (see column 8, lines 60 and 61 and column 12) and it is known that a cloning process must used a ligase, according to the definition of

"recombination protein" in the specification, the digested mutagenized double-stranded polynucleotide taught by Stemmer is an integration sequence-containing nucleic acid molecule comprising at least first and second recombination sites as recited in claim 16 wherein 5' and 3' ends of restriction sites of the digested mutagenized double-stranded polynucleotide are a first and a second recombination site and Stemmer discloses causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., a ligase) as recited in claim 16. Since Stemmer teaches that 5' and 3' ends of restriction sites of the digested mutagenized double-stranded polynucleotide are a first and a second recombination site, Stemmer discloses that said first and second recombination sites are separated by a portion of said integration sequence-containing nucleic acid molecule as recited in claim 18.

Regarding claims 15 and 27, since double-stranded random fragments are generated from a PCR product of the wild-type LacZ alpha gene (see column 11), the double-stranded random fragments are genomic DNA as recited in claims 15 and 27.

Regarding claim 17, since an appropriate vector taught by Stemmer is a plasmid such as pUC 18 (see column 12, lines 13-67) and it is known that a plasmid is a circular molecule, Stemmer discloses that said recombination of said first and second recombination sites insert into the vector and results in a circular molecule as recited in claim 17.

Regarding claims 19 and 20, since the oligonucleotides comprising one or more mutations taught by Stemmer can be single stranded and it is known that a single stranded nucleic acid can be labeled with P^{32} at the 5' end in the presence of T4 polynucleotide kinase. According to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), selectable markers are DNA segments that bind

products that modify a substrate, the oligonucleotides comprising one or more mutations taught by Stemmer are DNA segments that bind product that modify a substrate (ie., T4 polynucleotide kinase) or one or more selective markers as recited in claims 19 and 20.

Regarding claims 32 and 33, since Stemmer teaches that said first and second recombination sites are 5' and 3' ends of restriction sites (see above), Stemmer discloses that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33.

Regarding claim 44, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches to digest a PCR product with restriction enzymes BamHI and Eco0109 and ligates digested PCR product into pUC18 digested with BamHI and Eco0109 (see column 12, lines 6-67). Since 3' and 5' of the digested PCR product taught by Stemmer has restriction sites, Stemmer discloses a first nucleic acid molecule comprising at least a first segment which comprises at least a first and a second recombination site (ie., 3' and 5' restriction sites of the digested PCR product), wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since 5' and 3' ends of pUC18 contain restriction sites, Stemmer discloses a second nucleic acid molecule comprising at least a third

and fourth recombination site (ie., 5' and 3' restriction sites of pUC18) as recited in steps (b) and (c) of claim 44. Since, during the ligation reaction, the digested PCR product must mix with pUC18 digested with BamHI and Eco0109 in the presence of a ligase, Stemmer discloses forming a mixture by mixing said first nucleic acid molecule (ie., the digested PCR product with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., pUC18 digested with BamHI and Eco0109) in the presence of at least one recombination protein (ie., a ligase) and incubating said mixture under conditions favoring recombination at least between said first (ie., the BamHI site on the digested PCR product) and third recombination sites (the BamHI site on the digested pUC18) and at least between said second (ie., the Eco0109 site on the digested PCR product) and fourth recombination sites (ie., the Eco0109 site on the digested pUC18), thereby transferring said first segment (ie., the digested PCR product) from said first nucleic acid molecule to said second nucleic molecule (ie., the digested pUC18) as recited in steps (b) and (c) of claim 44.

Regarding claims 45 and 46, since 3' and 5' of the digested PCR product taught by Stemmer has restriction sites (see above), Stemmer teaches that said first segment (ie., the digested PCR product) is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited in claim 45 wherein said first, second, third and fourth recombination sites are site-specific recombination sites as recited in claim 46.

Regarding claim 57, since the ligation reaction taught by Stemmer is performed in *in vitro* (see column 12, lines 6-67), Stemmer discloses that said recombination (ie., the ligation taught by Stemmer) takes place *in vitro* as recited in claim 57.

Therefore, Stemmer teaches all limitations recited by claims 14-20, 27, 32, 33, 44-46, and

57.

6. Claims 14-20 , 27, 32, 33, 44-46, 56, 57-59, 69, and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Atlung *et al.,* (Gene 107, 11-7, October 1991).

Atlung *et al.,* teach a versatile method for integration of modified genes and gene fusions into the bacteriophage lambda attachment site (attB) of the *Escherichia coli* chromosome.

Regarding claims 14, according to the specification, integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). "mobile genetic element" is defined as an element of genetic material that has the ability to move genetic material within and between organisms. "mobile genetic elements" include all plasmids, viruses, transposons, insertion sequences, and other classes of elements with these general properties (see attached "mobile genetic element"). Atlung *et al.,* teach to construct phoA region of pTAC3575 by inserting the aphA gene from TnphoA and construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sma I site of pTAC3575 (see Figure 1 in page 12 and left column in page 13). Since the insertion sites of the aphA gene from TnphoA are recombination sites, Atlung *et al.,* disclose inserting one or more mobile genetic elements comprising at least one recombination

site (ie., aphA gene from TnphoA) into at least one nucleic acid molecule (ie., pTAC3575 having phoA from plasmid pBR 322) to produce one or more mobile genetic elements-containing nucleic acid molecules (ie., pTAC3575 having phoA from phA gene of TnphoA) as recited in claim 14 wherein said mobile genetic elements is transposon (ie., aphA gene from TnphoA) as recited in claims 58 and 59. Since Atlung *et al.,* teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see page 13, left column and Figure 2 in page 14) and it is known that a ligation reaction must be performed in the presence of a ligase, Atlung *et al.,* disclose transferring one or more mobile genetic elements-containing nucleic acid molecules (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) comprising recombination sites (ie., restriction sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) into one or more vectors (ie., the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) in the presence of one or more recombination proteins (ie. the ligase) as recited in claim 14.

Regarding claims 16 and 18, according to the specification, integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page

25, second paragraph). "mobile genetic element" is defined as an element of genetic material that has the ability to move genetic material within and between organisms. "mobile genetic elements" include all plasmids, viruses, transposons, insertion sequences, and other classes of elements with these general properties (see attached "mobile genetic element"). Atlung *et al.,* teach to construct phoA region of pTAC3575 by inserting the aphA gene from TnphoA, construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sma I site of pTAC3575, ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see Figure 1 in page 12, page 13, left column and Figure 2 in page 14). Since the insertion sites of the aphA gene from TnphoA are recombination sites, Atlung *et al.,* disclose inserting one or more mobile genetic element comprising at least one recombination site (ie., the aphA gene from TnphoA) into at least one nucleic acid molecule (ie., pTAC3575) as recited in claim 16. Since it is known that a ligation reaction must be performed in the presence of a ligase, a nucleic acid molecule that is produced by inserting one or more mobile genetic elements comprising at least one recombination site (ie., the aphA gene from TnphoA) into at least one nucleic acid molecule (ie., pTAC3575) and the aphA gene from TnphoA taught by Atlung *et al.,* comprises at least first and a second recombination sites as recited in claim 16, Atlung *et al.,* disclose causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., the ligase) as recited in claim 16 wherein said first and second recombination sites are separated by a portion of said mobile genetic element-containing nucleic acid molecule as recited in claim 18.

Regarding claims 15 and 27, Atlung *et al.*, teach that said nucleic acid molecule (ie., the aphA gene from TnphoA) is genomic DNA as recited in claims 15 and 27.

Regarding claim 17, Since Atlung *et al.*, teach to construct phoA region of pTAC3575 by inserting the aphA gene from TnphoA (see page 13, left column and Figure 2 in page 14), Atlung *et al.*, disclose that said recombination of said first and second recombination sites results in a circular molecule as recited in claim 17.

Regarding claims 19 and 20, Atlung *et al.*, teach that said integration sequence comprises one or more genes or portions of genes (ie., the aphA gene from TnphoA) as recited in claims 19 and 20.

Regarding claims 32 and 33, since Atlung *et al.*, teaches to construct phoA region of pTAC3575 by inserting the aphA gene from TnphoA in order to replace phoA from pBR 322 (see page 13, left column), Atlung *et al.*, discloses that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33.

Regarding claims 44, 56, 69, and 70, according to the specification, integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). "mobile genetic element" is defined as an element of genetic material that has the ability to move genetic material within and between organisms. "mobile genetic

elements" include all plasmids, viruses, transposons, insertion sequences, and other classes of elements with these general properties (see attached "mobile genetic element"). Atlung *et al.,* teach to construct phoA region of pTAC3575 by inserting the aphA gene from TnphoA, construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sama I site of pTAC3575, ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see Figure 1 in page 12, page 13, left column and Figure 2 in page 14). Since Atlung *et al.,* teach to generate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene from the aphA gene of TnphoA and the appYp-lacz fusion, Atlung *et al.,* disclose obtaining a first nucleic acid molecule comprising at least a first segment (ie., purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) which comprises at least a first and a second recombination site (ie., BstE II and Xho I sites) wherein said segment comprises at least one mobile genetic element as recited in step (a) of claim 44 wherein said mobile genetic element is a transposon (ie., the phoA gene from the aphA gene of TnphoA). Since Atlung *et al.,* teach the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463, Atlung *et al.,* disclose a second nucleic acid molecule comprising at least third and fourth recombination sites (ie., BstEII and Sal I sites) as recited in step (b) of the claim. Since, during the ligation reaction, the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion must mixed with the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 in the presence of a ligase, Atlung *et al.,* disclose forming a mixture by mixing said first nucleic acid molecule (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz

fusion) with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) in the presence of at least one recombination protein (ie., the ligase), and incubating said mixture under conditions favoring recombination at least between said first (ie., BstE II site from the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) and third recombination sites (ie., BstE II site from the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) and at least between said second (ie., Xho I site from the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) and fourth recombination sites (ie., Sal I site from the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) thereby transferring said first segment (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) from said first nucleic acid molecule to said second nucleic molecule as recited in steps (b) and (c) of claim 44. Since Atlung *et al.,* teach to select colonies with the cassette integrated into the attB site of the E. Coli chromosome (see page 11, abstract), Atlung *et al.,* teach selecting for the second nucleic acid molecule comprising said transferred first segment as recited in claim 56.

Regarding claims 45 and 46, since 3' and 5' of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.,* has restriction sites (see above), Atlung *et al.,* teaches that said first segment (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) is flanked on one side by said first recombination site and is flanked on the other side by said second

recombination site as recited in claim 45 wherein said recombination sites are site-specific recombination sites as recited in claim 46.

Regarding claim 57, since the ligation reaction taught by Atlung *et al.,* is performed in *in vitro* (see Table 1 in page 13 and Figure 2 in page 14), Atlung *et al.,* discloses that said recombination (ie., the ligation taught by Atlung *et al.,*) takes place in vitro as recited in claim 57.

Therefore, Atlung *et al.,* teach all limitations recited in claims 14-20, 27, 32, 33, 44-46, 57-59, 69, and 70.

7. Claims 14-20, 27, 32-51, 56-59, 69, and 70 are rejected under 35 U.S.C. 102(a) or 102 (e) as being anticipated by Hartley *et al.,* (US Patent No. 5,888,732, filed on June 7, 1996 and published on March 30, 1999).

Hartley *et al.,* teach recombinational cloning using engineered recombination sites.

Regarding claims 14, 58, and 59, according to the specification, integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). "mobile genetic element" is defined as an element of genetic material that has the ability to move genetic material within and between organisms. "mobile genetic

elements" include all plasmids, viruses, transposons, insertion sequences, and other classes of elements with these general properties (see attached "mobile genetic element"). Hartley *et al.,* teach a method of making chimeric DNA, which comprises: (a) combining *in vitro* or *in vivo* (i) an Insert Donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site, wherein the first and second recombination sites do not recombine with each other; (ii) a Vector Donor DNA molecule containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination sites do not recombine with each other; and (iii) one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and fourth recombinational sites; thereby allowing recombination to occur, so as to produce at least one Cointegrate DNA molecule, at least one desired Product DNA molecule which comprises said desired DNA segment, and optionally a Byproduct DNA molecule; and then, optionally, (b) selecting for the Product or Byproduct DNA molecule (see column 4, lines 47-67, column 5, line 1, and Figures 1, 2A, 3A, and 4A). Since Hartley *et al.,* teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site and tetOP which is operator/promoter from transposon Tn 10 (see column 6), Hartley *et al.,* disclose one or more mobile genetic element comprising at least one recombination site as recited in claim 14 wherein said mobile genetic element is a transposon as recited in claims 58 and 59. Since Hartley *et al.,* teach to form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of an Insert Donor DNA molecule, a Vector Donor DNA molecule, and one or more site specific recombination proteins, Hartley *et al.,* disclose inserting one or more mobile genetic element comprising at least one

recombination site (ie., an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site and tetOP (operator/promoter from transposon Tn 10)) into at least one nucleic acid molecule (ie., the Vector Donor DNA molecule taught by Hartley *et al.,*) to produce one or more integration sequence-containing nucleic acid molecules as recited in claim 14. Since Hartley *et al.,* teach that, in the presence of a recombinase, the Cointegrate DNA molecule further forms least one desired Product DNA molecule which comprises said desired DNA segment with recombination sites (ie., attR and loxP in Figure 2A) and optionally a Byproduct DNA molecule (see Figures 1 and 2A), Hartley *et al.,* disclose transferring one or more mobile genetic element-containing nucleic acid molecules comprising recombination sites (ie., a nucleic acid from the Cointegrate DNA molecule with attR and loxP and tetOP) into one or more vectors (ie., intprod in Figure 2) in the presence of one or more recombination proteins as recited in claim 14.

Regarding claim 16, since Hartley *et al.,* teach to insert an Insert Donor DNA molecule into a Vector Donor DNA molecule and form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of one or more site specific recombination proteins wherein the Insert Donor DNA molecule comprises a desired DNA segment flanked by a first recombination site and a second recombination site and tetOP which is operator/promoter from transposon Tn 10 (see columns 4 and 6, lines 46-67 and Figures 1, 2A, 3A, and 4A), Hartley *et al.,* disclose inserting one or more mobile genetic element (ie., the Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site and tetOP taught by Hartley *et al.,*), said one or more integration sequences comprising at least one recombination site, into at least one nucleic acid molecule (ie., Vector

Donor DNA molecule taught by Hartley *et al.*,) thereby producing a mobile genetic element-containing nucleic acid molecule (ie., pEZC7cointegr in Figure 2) comprising at least a first and a second recombination site (ie., attR and loxP); and causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., Cre in Figure 2) as recited in claim 16.

Regarding claims 15 and 27, since Hartley *et al.*, teach that pEZC726 contains kanamycin resistance gene, Hartley *et al.*, disclose that said nucleic acid molecule is genomic DNA or cDNA as recited in claims 15 and 27.

Regarding claims 17 and 18, since Hartley *et al.*, teach the first and second recombination sites of pEZC705 (ie., attB and loxP) recombine with the third and fourth recombination sites of pEZC726 (ie., attP and loxP) to form pEZC7 cointegr (see Figure 2A), Hartley *et al.*, disclose that said recombination of said first and second recombination sites results in a circular molecule as recited in claim 17 wherein said first and second recombination sites (ie., att R and loxP) are separated by at least a portion of said mobile genetic element (ie., tetOP)-containing nucleic acid as recited in claim 18 (see pEZC705 in Figure 2A).

Regarding claims 19 and 20, since the mobile genetic element (ie., the Insert Donor DNA molecule such as pEZC726) taught by Hartley *et al.*, has kan (a kanamycin resistance gene), according to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), Hartley *et al., et al.*, disclose that said integration sequence comprises one selectable marker (ie., kan) as recited in claims 19 and 20.

Regarding claims 32-39, since Hartley *et al.*, teach that the first and second

recombination sites are attR and loxP respectively (see pEZC7cointegr in Figure 2A), Hartley *et al.*, disclose that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33, said recombination sites are selected from the group consisting of loxp, attB, attp, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism, or mutants or derivatives thereof as recited in claim 34, said recombination sites are selected from the group consisting of loxP, attB, attP, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism as recited in claim 35, at least one of said first and said second recombination sites is an att site or a mutant or derivative thereof as recited in claim 36, at least one of said first and said second recombination sites is an att site as recited in claim 37, said att site is selected from the group consisting of attB, attP, attL and attR, or a mutant or derivative thereof as recited in claim 38, said att site is selected from the group consisting of attB, attP, attL and attR as recited in claim 39.

Regarding claims 44, 69, and 70, since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site and tetOP which is operator/promoter from transposon Tn 10 (see column 6), Hartley *et al.*, disclose obtaining a first nucleic acid molecule (ie., the Insert Donor DNA such as pEZC726 having tetOP) comprising at least a first segment which comprises at least a first and a second recombination site (ie., a desired DNA segment flanked by a first recombination site and a second recombination site) wherein said segment comprises at least one mobile genetic

element as recited in step (a) of claim 44 wherein said mobile genetic element is transposon as recited in claims 70 and 71. Since Hartley *et al.,* teach to insert an Insert Donor DNA molecule into a Vector Donor DNA molecule and form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and fourth recombinational sites wherein the Vector Donor DNA molecule containing a third recombination site and a fourth recombination site and tetOP which is operator/promoter from transposon Tn 10 (see column4, lines 46-67, column 6, and Figures 1, 2A, 3A, and 4A), Hartley *et al.,* disclose forming a mixture by mixing said first nucleic acid molecule (ie., the Insert Donor DNA molecule taught by Hartley *et al.,*) with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., the Vector Donor DNA molecule taught by Hartley *et al.,*) in the presence of at least one recombination protein, and incubating said mixture under conditions favoring recombination at least between said first and third recombination sites and at least between said second and fourth recombination sites, thereby transferring said first segment from said first nucleic acid molecule (ie., see nucleic acid segment from pEZC726 in PEZC7cointegr in Figure 2) from to said second nucleic molecule (ie., the Vector Donor DNA molecule taught by Hartley *et al.,*) as recited in claim 44.

Regarding claim 45, since Hartley *et al.,* teach that there is a nucleic acid segment between attB (ie., a first recombination site) and loxP (ie., a second recombination site), Hartley *et al.,* disclose said first segment is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited by claim 45.

Regarding claims 46-51, since Hartley *et al.,* teach that the first and second

recombination sites are attB and loxP respectively (see pEZC705 in Figure 2A), Hartley *et al.*, disclose that said first and second recombination sites are site-specific recombination sites as recited in claim 46, said recombination sites are selected from the group consisting of loxP, attB, attP, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism as recited in claim 47, at least one of said first and said second recombination sites is an att site or a mutant or derivative thereof as recited in claim 48, at least one of said recombination sites is an att site as recited in claim 49, said att site is selected from the group consisting of attB, attP, attL and attR, or a mutant or derivative thereof as recited in claim 50, said att site is selected from the group consisting of attB, attP, attL and attR as recited in claim 51.

Regarding claim 56, Hartley *et al.*, teach selecting for the second nucleic acid molecule comprising said transferred first segment (ie., the product DNA molecule) (see column 4, lines 46-65 and column 5, line 1).

Regarding claim 57, since the recombination reaction taught by Hartley *et al.*, is performed in vitro (see column 4, lines 46-67), Hartley *et al.*, disclose that said recombination takes place in vitro as recited in claim 57.

Therefore, Hartley *et al.*, teach all limitations recited in claims 14-20, 27, 32-39, 44-51, 56-59, 69, and 70.

Response to Arguments

In page 14 bridging to page 17 of applicant's remarks filed on July 22, 2005, applicant argues that: (1) in view of the page 22, line 29 to page 23, line 3 of the specification, applicants

respectfully point out that it is clear from the specification of the captioned application what is meant by the term "mobile genetic element". In particular, the specification defines mobile genetic element and it is unnecessary to look to a dictionary or other extrinsic source to determine the meaning of this claim element; (2) "the definition cited by the Examiner is actually a definition for the term 'transposable genetic element,' not the term 'mobile genetic element,' which is recited in the claims. Although the cited webpage suggests that the term 'mobile genetic Element' is a synonym for 'transposable genetic element' according to the definition provided in the present specification, a 'transposable element' is defined as a type of mobile genetic element. See Specification at page 23, lines 1-4. Applicants respectfully submit that it is improper for the Examiner to ignore the definition of 'mobile genetic element' provided in the specification in favor of a definition gleaned from an Internet glossary"; (3) "[E]ven adopting the Examiner's definition of 'mobile genetic element,' the rejections under 35 U.S.C. § 102 should be withdrawn. The Examiner's definition recites that this is '(a) general term for any genetic unit that can insert into a chromosome, exit, and relocate.' See (http//www. biochmem.northwestern.edu/holmgrenGlossory/Definition/Def-T/transposable_genetic_ element_.html), attached to the withdrawn Advisory Action (emphasis added). However, nucleic acid fragments produced, for example, by restriction digest or by random fragmentation are not, simply by virtue of being a nucleic acid fragment, capable of performing all three operations recited in the Examiner's definition of 'mobile genetic element'; namely, inserting into a chromosome, exiting, and relocating"; and (4) "[T]he definition of 'mobile genetic element' cited by the Examiner in the Advisory actions does not establish that any of Stemmer[2], Atlung[3], or Hartley[4], over which the Examiner has maintained the rejections under 35 U.S.C. §102,

disclose all of the elements of the claimed invention, as required for a case of anticipation under 35 U.S.C. § 102. Hence, Applicants respectfully maintain that none of Stemmer, Atlung, or Hartley describes, either expressly or inherently, a method of introducing recombination sites into a nucleic acid molecule by inserting mobile genetic elements) comprising recombination sites as in the present claims".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in claim 14 (see above rejection). Since integration sequences are equal to mobile genetic element as argued by applicant (see above arguments), Stemmer teaches all limitations recited in claims 14-20, 27, 32, 33, 44-46, and 57. Second, since mobile genetic elements include transposon and both Atlung *et al.,* and Hartley *et al.,* teach transposon (see above rejection), both Atlung *et al.,* and Hartley *et al.,* disclose mobile genetic elements.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 14-20, 27, 32-39, 44-51, 57-59, 69, and 70 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-39 of U.S. Patent No.5,888,732. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but examined claims in this instant application are not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although independent claims 14-20, 27, 32-39, 44-51, and 57 in this instant application are not identical to claims 27-39 of U.S. Patent No.5,888,732, 27-39 of U.S. Patent No.5,888,732 are directed to the same subject matter and fall entirely within the scope of claims 14-20, 27, 32-39, 44-51, and 57 in this instant application. In other words, claims 14-20, 27, 32-39, 44-51, and

57 in this instant application are anticipated by claims 27-39 of U.S. Patent No. 5,888,732. Since the content of the specification indicate that an Insert Donor DNA contains a mobile genetic element (see column 6), claims 58, 59, 69 and 70 are anticipated by claims 27-39 of U.S. Patent No. 5,888,732. Note that applicant does not address this issue in applicant's remarks filed on July 22, 2005.

Conclusion

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

(1) The prior art that can be used for rejections under 35 U.S.C. 102(e) and double patenting:

Hartley et al., (U.S. Patent Nos. 6,171,861 B1, 6,270,969, and 6,277,608)

(2) The prior art that can be used for rejections under 35 U.S.C. 102(e):

Hartley et al., (U.S. Patent No. 6,143,557)

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Frank Lu
Primary Examiner
March 6, 2006

FRANK LU
PRIMARY EXAMINER